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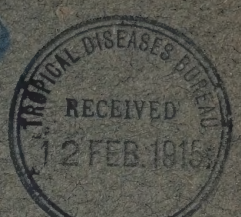
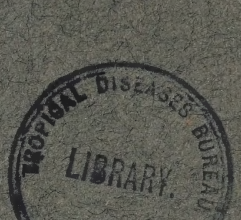


EPIDEMIC OR FULMINANT MALARIA TOGETHER WITH A PRELIMINARY STUDY OF THE PART PLAYED BY IMMUNITY IN MALARIA



BY

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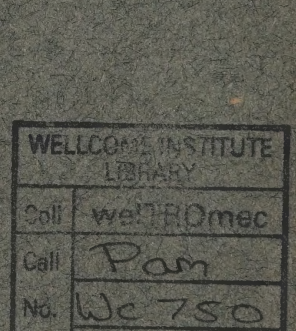

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EPIDEMIC OR FULMINANT MALARIA TOGETHER WITH A PRELIMINARY STUDY OF THE PART PLAYED BY IMMUNITY IN MALARIA.

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1.—INTRODUCTION.

MALARIA manifests itself in a community in a variety of ways. We speak of endemic, epidemic, pandemic, and autumnal epidemic, or fulminant malaria and we refer to areas being moderately endemic, highly endemic and hyper-endemic centres of infection.

It is necessary to know with precision what is implied by these terms and it will, therefore, be convenient here to define the exact significance of the nomenclature it is proposed to adopt in this study of the epidemiology of malaria.

In regard to endemic malaria, this expression will be restricted to that implied in the etymological derivation of the word "endemic," that is to say endemic malaria will be merely held to imply the constant presence of reservoirs of malarial infection in a community. For reasons which will appear later, a different significance is to be attached to endemic malaria according to the geographical position of the affected area. Endemic malaria will, therefore, be subdivided into (A) Tropical malaria and (B) Subtropical malaria. These subdivisions into tropical and subtropical are made irrespective of the situations of the Tropics of Cancer and Capricorn, and they are used to denote, in the case of tropical malaria, the occurrence of malaria in areas where, owing to the

tropical nature of the climate, malarial infections may occur throughout the year. Subtropical malaria, on the other hand, will be held to imply the occurrence of malaria in areas where malarial infection can only be contracted during a portion of the year. Reasons will also be deduced to show that the terms " healthy," " moderately endemic," " highly endemic," and " hyper-endemic," which are held to imply a spleen-rate of under 10 per cent., 10-25 per cent., 25-50 per cent. and over 50 per cent. respectively, can only usefully be employed in connexion with tropical malaria as defined above.

Epidemic malaria, which term appears to be somewhat vaguely used at present, will be considered to connote the occurrence in endemic areas or an exaggeration of the normal incidence of the disease together with a moderate increase in its mortality.

In most paludic countries mild epidemics of a generalised nature occur from time to time and certain years are consequently spoken of as " bad fever years." Localised epidemics may also occur, such, for example, as those associated with the so-called " tropical aggregation of labour." Epidemic malaria may, therefore, be subdivided into (A) Generalised epidemic malaria, (B) Localised epidemic malaria.

In addition to the above, we know, chiefly as the result of the researches of Christophers(1), that malaria may assume almost pandemic proportions together with a virulence greatly in excess of normal. This he termed " autumnal epidemic or fulminant malaria." Celli, (2) however, as long ago as 1900 recorded the occurrence in Italy of pandemic malaria which appears to be in all respects identical with the fulminant malaria of Christophers. Outbreaks of malaria of this nature will be considered to imply the widespread occurrence in endemic areas of malaria of cyclical epidemics of so violent and explosive a nature as to involve the major portion of the population and to cause a mortality many times that of normal years.

The word " pandemic " as applied to this form of malaria does not seem strictly appropriate, since pandemic malaria does not tend to spread beyond the immediate neighbourhood of its endemic areas and, moreover, Christophers states that it exhibits its greatest intensity in those communities which show a high degree of endemicity. The pandemic form of other diseases, such as plague, cholera and influenza, on the other hand, are characterised by rapid diffusion beyond their endemic limits and by the fact that the endemic areas themselves are but slightly affected by the pandemic.

It is proposed, therefore, to discard Celli's appellation of pandemic malaria and to substitute the term fulminant malaria (originally given to it by Christophers) which, in addition to being free from the above objection, also serves to suggest its violent and explosive nature.

To summarise, malaria, from the epidemiological standpoint, requires consideration in its aspect as :—

(A). An endemic disease	..	(1) In the tropics.
		(2) In the subtropics.
(B). An epidemic disease	..	(1) Fulminant epidemics.
		(2) Localised epidemics.
		(3) Generalised epidemics.

Whilst for the moment it is expedient to emphasise the distinctive nature of these various manifestations of the same disease, their mutual relationship will subsequently become apparent. In particular, it will be seen from the definitions given above that the difference between a generalised epidemic and fulminant malaria is chiefly one of degree. It will be shown later, however, that their classification as separate entities is both justified and justifiable on other grounds.

II.—The Nature of Fulminant Malaria.

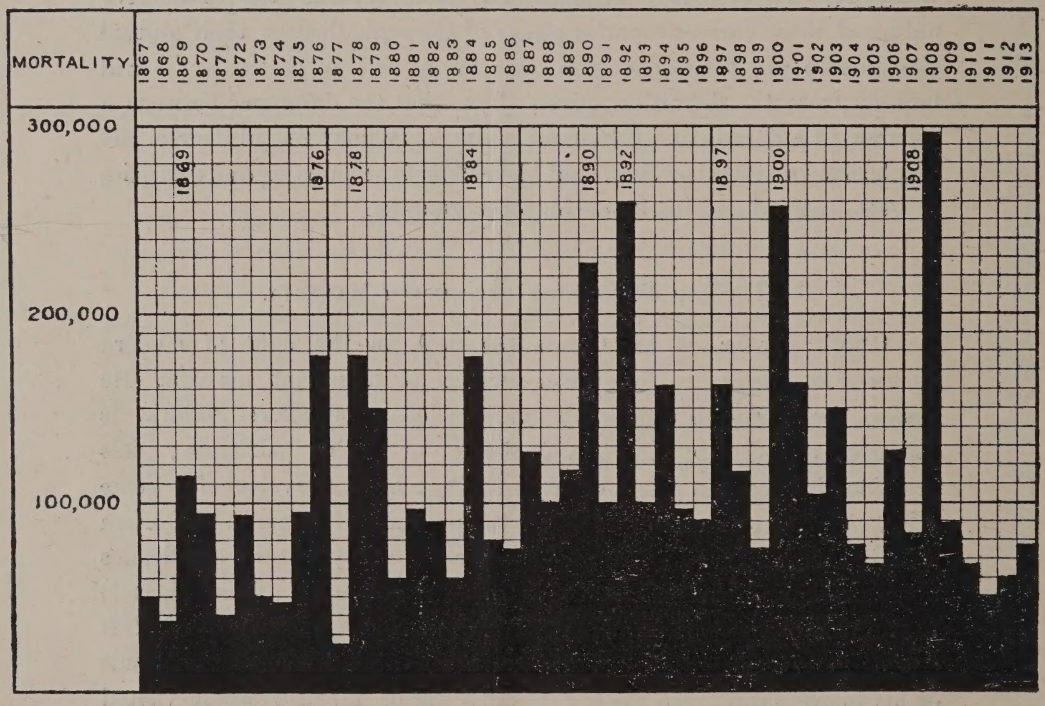
Celli(3) appears to have been the first, in the light of modern scientific knowledge, to note the occurrence of fulminant malaria. He states " from time to time in the various localities where malaria is endemic, the disease becomes epidemic or even pandemic ; this occasionally occurs in places where it had not been prevalent for some time. We had an example of this in the province of Rome in 1879 when a true malarial pandemic raged." No precise study of these pandemics appear to have been made and it is to the researches of Christophers(1) that our knowledge of fulminant malaria is almost entirely due. This author in his monograph " Malaria in the Punjab " records the result of his investigation into the severe outbreak of malaria which visited the Punjab in 1908. In the autumn of this year, it may be recalled, there occurred with remarkable suddenness throughout a large portion of the Punjab an epidemic of such extraordinary severity as to involve almost the entire population and, in areas where the epidemic was severely felt, to cause a mortality rate of several hundreds per thousand. So unusual did this state of affairs appear that many people doubted the true malarial nature of the epidemic ; or at least it was concluded that it

was malaria complicated by some other disease such as dysentery, or that it was associated with some unusual form of parasite.

Christophers, however, was able to prove conclusively, not only that the outbreak was an uncomplicated epidemic of malaria associated with the parasites that are constantly prevalent in the Province, but that outbreaks of an apparently identical nature and of almost equal severity have occurred periodically in the past. This is well shown in the Chart (Chart 1).

CHART I.

Fever mortality (October and November deaths) in the Punjab during the years 1867-1913.



It will thus be seen that the fever mortality (October and November deaths) in the Punjab shows remarkable oscillations and it is clear that, in addition to that of 1908, severe outbreaks of a similar nature have occurred in previous years.

In regard to the nature of the 1908 outbreak, of which alone we possess precise knowledge, I cannot do better than quote, in his own words, the more important conclusions arrived at by Christophers(1).

He summarises them as follows :—

(1) Malaria in the Punjab is manifested in two ways, namely, as "endemic malaria" and as "autumnal epidemic or fulminant malaria."

(2) Economically the latter is by far the most important and it is to the effects of this form which are usually referred to when the disastrous results of malaria in the Punjab are spoken of.

(3) The epidemic of 1908 was of this character and there have been similar epidemics at intervals at least as far back as the sixties.

(4) These epidemics are focal, that is their effects are greatest in the centre of the epidemic area and fade towards the periphery.

(5) The history of past epidemics shows that they affect all parts of the submontane tract, but have a special frequency over certain areas. In 1908 there existed, for the first time, two distinct major epidemic areas, the southern one producing epidemic effects also over the western half of the United Provinces.

(6) Epidemic malaria attacks most severely those communities which already show a high degree of endemic malaria. It is, therefore, not merely the result of malaria attacking those unaccustomed to the disease, nor are endemic areas in any way protected against it.

(7) The most salient feature of the epidemic condition is the excessive mortality and its conspicuously infantile character.

(8) Towns and cities suffer equally with, even in some cases more than, rural areas, and even the centres of large cities are only moderately protected from epidemic effects.

(9) The determining causes of epidemics are excessive rainfall and scarcity ; the former is an essential whilst the latter is an almost equally powerful influencing factor.

(10) When epidemic areas are examined in detail the villages are found to have suffered almost exactly in proportion as they have been flooded. Floods act equally whether they are due to local rain or to the indirect effects of rain causing the overflow of rivers. Fulminant malaria of a certain intensity is almost synonymous with malaria of diluvial origin.

(11) The exact mechanism of epidemic causation is still unknown. But the epidemic condition appears to be due to an excessive seasonal increase in the normal parasite rate, fluctuations in which occur even in healthy years.

(12) Physical features influence epidemics and low waterlogged areas are especially susceptible to epidemic conditions. Higher tracts, on the contrary, are comparatively less susceptible. But these differences are often lost when a district becomes involved in the nucleus of an epidemic area.

(13) Experiments on sparrows and proteosoma show that severity of infection is largely dependent on the dose inoculated. This is not merely the result of the number of infected mosquitos, but of the number of sporozoits injected at each bite. This in turn depends on the number of gametes in the blood of the original sparrow by which the mosquito was infected.

(14) No observations exist as to the conditions in regard to anopheles at epidemic times, but the close association of fulminant malaria with actual flooding suggests something more than the ordinary reproduction of the genus in pools.

Whilst, therefore, the characteristics of fulminant malaria are well defined, no adequate explanation appears to have been offered of the remarkable phenomenon of a disease, ordinarily of a chronic debilitating nature, manifesting itself in such a violent and explosive manner as to cause mortalities of almost unprecedented proportions.

Celli(4) has suggested that these periodic waves of intensity and prevalence of malaria may be due to the development and exhaustion of the degree of immunity possessed by the population. He also adds that no relationship has been established between meteorological conditions and epidemic malaria, and he puts forward the suggestion that the latter may be due to general biological properties inherent in the specific parasites themselves rather than to climatic reasons. Christophers(1) comes practically to the same conclusion. He states, as we have seen, that the epidemic condition appears to be due to an excessive seasonal increase in the parasite rate, fluctuations in which occur even in healthy years. Both these authorities, however, are silent in regard to the factors, determining, on the one hand, fluctuations in the collective immunity of the population and, on the other, oscillations in

the parasite rate. In regard to the possible part played by immunity, Christophers, in reference to the Punjab epidemic, shows that the most malarious localities were affected by the epidemic to a relatively greater extent than more healthy areas and he concludes that immunity can play little or no part in the production of fulminant malaria. On the other hand, he shows that fulminant malaria is intimately associated with excessive rainfall (or flooding) and scarcity. But these conditions are not peculiar to the Punjab and there is nothing distinctive about them to determine the occurrence of fulminant malaria in that province in contradistinction to malaria in other parts of India. Indeed, Christophers himself states that the eastern half of the United Provinces in 1908 received not only more rain but even a greater excess over normal than the western half, in spite of which the latter alone was affected by the fulminant epidemic. Again, the rainfall and scarcity factors, the combined importance of which Christophers strongly emphasises, must, occasionally at least, be in operation in Bombay city to an equal extent to that experienced in northern India. Yet Bentley(5) expressly states that in the latter city, although there is apt to be from time to time a slight autumnal increase in malaria, 'there is no evidence to show that outbreaks of malaria have ever been of so severe a nature as the pandemics that occur in the Punjab."

Sir Ronald Ross(6) remarks on this subject: "In low latitudes the temperature is generally uniformly hot all the year round, so that the anophelines should be able to breed at all seasons, especially where the rainfall is fairly evenly distributed. But in higher latitudes the breeding can only occur in the short hot weather. Hence we should infer that the anopheline factor must always be higher in the former and the malaria more abundant. But statistics often show that just the opposite happens." And he instances the north of India, that is to say, the Punjab. He suggests as a possible explanation that anophelines with a high "carrying-power" do not breed best in a uniformly warm temperature. This theory is not altogether convincing since the mosquito fauna of the Punjab are not distinctive, indeed the common malaria-carriers are the same species that ordinarily "carry" malaria in parts of India where fulminant malaria is unknown.

Bentley(7) has recently advanced the view that epidemic malaria, or what is here called fulminant malaria, is the result of a sudden change in environment on the part of the human factor converting favourable into unfavourable conditions. Such changes, he suggests, may follow

the introduction of an unfamiliar parasite, the influence of unusual seasons, or be the result of the disturbance produced amongst primitive parasite-harbouring races by advancing civilisation.

These surmises, so far as fulminant malaria in the Punjab is concerned, receive little support from the facts. In the first place, Christophers(1) has shown that the 1908 outbreak was not associated with the introduction of an unfamiliar parasite. Again, the influence of unusual seasons is a factor in operation to a greater or less degree throughout the world and it cannot, therefore, be held to be responsible for the restricted geographical distribution of these epidemics. The same criticism applies to the effect of social dislocations occasioned by the advance of civilisation.

The conclusion, therefore, reached as a result of this brief review of the scanty literature of fulminant malaria is that, whilst the mechanism of its causation is unknown, opinion is inclined to attribute, chiefly on theoretical grounds, a predominant influence either to biological properties inherent in the malarial parasite or to unknown circumstances affecting the susceptibility of its human host.

But until these explanations have themselves been explained and the fundamental principles governing the occurrence of these outbreaks have been established on a scientific basis no real advance in our knowledge of the epidemiology of malaria will be achieved.

III.—The History and Geography of Fulminant Malaria.

It is unreasonable to expect that a disease, widely endemic throughout the world, should exhibit in one quarter of the globe only, characteristics without parallel elsewhere. Nevertheless no exact counterpart of fulminant malaria as met with in northern India has, in modern times, been reported from other countries. Indeed, except in the case of Italy, little has been heard of malarial epidemics of the nature now under consideration. It must, however, be recollected that, although the 1908 outbreak in the Punjab was by no means the first of its kind, yet its occurrence had escaped recognition until Christophers established the facts in regard to the last of these Punjab epidemics. It, therefore, by no means follows that northern India has almost the unique distinction in modern times of exhibiting malaria in its most fatal form as a fulminant epidemic. Indeed, an examination of the literature of malaria strongly supports the view that fulminant malaria is apt to occur in many other quarters of the globe.

In regard to the past, accurate knowledge of fulminant epidemics is scanty, and much reliance cannot be placed on the accounts of ancient epidemics. Deaderick(8) and Craig(9), however, both state that malaria assumed pandemic form in Europe in 1557-1558, at which time endemic malaria was prevalent both on the Continent and in Great Britain. The former author also mentions subsequent European pandemics one of which is said to have occurred between the years 1806 and 1812. In 1809 a British Army of 25,000 men—the famous Walcheren expedition—was in the space of two months placed *hors de combat* by an epidemic of malaria. The expedition left England on July 28th, 1809, and it is stated by Melville(10) that early in September there were upwards of 7,000 men suffering from malaria in the various hospitals and that by the 14th of that month out of a strength of 15,000 in Walcheren 10,000 men were actually sick and 25—30 deaths were occurring daily. At this time, therefore, the morbidity was equal to an annual rate of 660 per mille and the mortality was upwards of 500 per mille. It will be noted—and the significance of this point will later become apparent—that the army consisted of a body of susceptible individuals who were operating in a country where malaria was endemic at the height of its "fever" season.

In the north of Europe malaria is rarely met with at the present day, but in the south it is widely prevalent throughout Spain, Italy, Greece, and in parts of France. In regard to Italy, as we have already seen, Celli(3) has recorded the occurrence of true pandemic malaria. He states that the mortality from malaria for the whole of Italy from 887 onwards has been the subject of regular periodic oscillations with a maximum every five or six years. The mortality statistics for this period do not show such marked periodic variations as occur in the Punjab, nevertheless this description, together with his definite statement that a great malaria pandemic raged in 1879, warrants the conclusion that true fulminant malaria occurs from time to time in parts of Italy. Celli also adds that similar epidemics have occurred in Greece, Hungary and Russia.

In regard to Greece, Professor Constantine Savas(11) states that in Greece, out of a total population of 2,631,962 inhabitants, an average of 770,000 are affected by malaria every year. He mentions, however, that in some years the number of cases is far heavier. Thus, for example, in 1905 more than half the inhabitants of the country were affected and over 6,000 died of the disease ; in many communes all the

inhabitants suffered. This condition of affairs vividly recalls fulminant malaria as met with in the Punjab.

In regard to Spain no definite facts are forthcoming. Macdonald(12), however, states that Spain has always suffered severely from malaria, and he adds that the records of history show that the disease has occasionally swept over this country with the virulence of plague.

I have been unable to find any record of epidemics in recent years in France, but in 1805 Deaderick(8) states an epidemic occurred at Bordeaux in which 12,000 persons were involved, of whom 3,000 died in the space of five months. The south of Europe may, therefore, be considered to exhibit, periodically, malaria epidemics of a distinctly fulminant type.

In 1911 Edmond and Etienne Sergent(13) recorded a severe epidemic of malaria in Algeria. Deaderick(8) also mentions the occurrence of malarial epidemics in this country. The Sergents, however, state that land excavations were being made in 1911 in connexion with defence works, so that it is possible that the epidemic should be placed under the category of epidemics associated with the aggregation of labour, rather than under the heading of fulminant malaria as defined above. No information is forthcoming in regard to fulminant epidemics in Morocco, Tunis or Tripoli. In Egypt Clemow(14) states that malaria is common, especially at the mouths of the Nile, and that it prevails extensively along its banks after the annual inundations begin to subside. In the light of what will shortly be put forward regarding the nature of fulminant malaria it is, however, a matter for surprise that no undoubted evidence of fulminant epidemics has been forthcoming from the Nile delta. At Khartoum, Balfour(15) states that locally acquired malaria is rare, whilst in Abyssinia, although it is known that malaria is prevalent, detailed information regarding its nature is wanting. The West Coast of Africa is notoriously the home of severe malaria and blackwater fever. Pernicious forms of the disease are common and many areas are uninhabitable by white races on account of its virulence. Clemow(14) states that in Senegal malaria becomes "violently epidemic each year at the end of the rainy season," and in Sierra Leone and in Gambia the conditions are said to be much the same. Indeed, the malarial history of most of the badly infected areas throughout tropical Africa, including the coast of Guinea, the Congo, British and German East Africa, is practically a repetition of the conditions reported from Senegal. There is no evidence in any of these countries that true fulminant malaria is ever met

with, for the occurrence of *annual* epidemics with an autumnal periodicity at once places them in a different category to the cyclical epidemics characteristic of fulminant malaria. That this apparently trivial distinction is not artificial, but has a real pathological significance, will become clear later, when it will be shown not only that fulminant malaria does not, but that it may be expected *not* to, occur in successive years in the same area. The true significance of these annual epidemics in tropical Africa will be demonstrated in their appropriate place. It is necessary here to call attention to the fact that much of our knowledge of the incidence of malaria in the tropics is derived from statistics dealing with the white population rather than with the native population amongst whom they live. This fact is of importance in the present connexion since an "epidemic" occurring, for example, amongst white troops stationed in a tropical country has a different significance to a widespread epidemic prevailing amongst the indigenous population. Passing south to Rhodesia and the Transvaal, we find in the words of Clemow(14) "nowhere in this part of the continent does malaria attain the extent or severity which characterise it on the West Coast and in certain regions in the interior of Central Africa," but he adds the significant sentence "its prevalence varies considerably in different years."

In the Transvaal severe malaria and blackwater fever occur in the veldt to the east and north of this colony. Bostock(16) states that the disease attracted little attention until the building of the Pretoria-Delagoa Bay Railway at which time localised epidemics of the type associated with the tropical aggregation of labour prevailed. In German South-West Africa Mannaberg(17) states that "intense malaria occurs." In Cape Colony malaria is a rare disease, but in the Orange River Colony, Clemow(14) states that "the floods to which some of the S. African rivers give rise after heavy rains lead *at times* to the prevalence of malarial fevers. This was the case in Gordonia in 1898, when ague became epidemic after severe floods caused by the Orange River in the month of January." South Africa being in the Southern Hemisphere the months of January and February are summer months, so that this epidemic occurred in the late summer or early autumn. In Natal malaria is prevalent, and Murison(18) records an extensive epidemic in Durban which commenced in January, 1905. The details in regard to this epidemic are of some interest. Murison states that the average annual number of cases of malaria in Durban previous to 1905 was seventy, all of whom were believed to have contracted the disease elsewhere.

Indeed, no definite information could be obtained to show that malaria had ever existed as a local infection in Durban before 1905; yet within a fortnight of the 1905 outbreak every medical man had recognised many cases. Certain anti-malarial measures were promptly carried out in the city with the apparent result that the epidemic speedily subsided. At the same time immediately outside Durban city every household, European and Native, was down with the disease, and the deaths, amongst Indians in particular, were enormous. In 1908, he states, no cases occurred in the city, but outside, where the disease had been rampant the previous year, and where no preventive measures of any kind had been taken, no fresh cases of malaria occurred. The disease, Murison adds, seemed to have suddenly left Durban country.

In the light of Christophers' researches it may be surmised that this epidemic was an example of fulminant malaria affecting a comparatively small area. The sudden onset of the epidemic and its spontaneous disappearance find their exact counterpart in the fulminant malaria of the Punjab.

In the Continent of Africa, therefore, whilst no evidence of true fulminant malaria can be discovered in the tropical zone, which is notoriously most severely infected by malaria, fulminant epidemics occur possibly in the north and almost certainly in the south.

In Madagascar malaria is prevalent in many areas, but no mention is made of epidemics. In 1905, however, a severe outbreak took place amongst the French troops operating in the island which is said by Clemow(14) to have caused over 6,000 deaths.

In Mauritius malaria was an unknown disease until 1857. During the first few years following its introduction a limited number of cases occurred, but from 1866-1869 a violent epidemic is stated to have swept through the island. No further epidemic has been recorded but malaria has since been reported by Davidson(19) to "dominate the pathology of the island" and to cause one-third of the entire mortality.

In view, moreover, of the extended period over which this epidemic is said to have continued it cannot be held to be a typical example of true fulminant malaria.

In Asia the occurrence of fulminant malaria has not been definitely recorded outside India; on the other hand, the disease has not been studied with precision in certain countries. Thus little information is forthcoming in regard to malaria in Siberia, Mongolia or Tibet. Parts of China are said to be intensely infected. Clemow(14) states in particular

that, in the valley of the Yangste-Kiang, malaria is especially active after the floods to which the river annually gives rise. He also records an epidemic at Chifu on the Straits of Pechili in the year 1895, but he adds that it was associated with the turning up of long undisturbed ground for road-making and building purposes.

In Korea malaria is the " predominating disease " in the spring and autumn.

In Formosa the aboriginal inhabitants are said to enjoy a relative immunity to malaria, the greatest sufferers being the Chinese, particularly those not born in the island, and the men of the Japanese garrisons. So far as the aboriginal inhabitants are concerned malaria epidemics are not recorded.

In regard to Afghanistan and Baluchistan little is known, but malaria is said to be intense in the swampy regions of those countries. In regard to Afghanistan, my assistant, Sub-Assistant Surgeon Ghulam Mohuddin, who has resided three years in that country, informs me that at Jellalabad and other places malaria epidemics of considerable severity occasionally occur in the autumn. In regard to Transcaspia and Russian Turkestan a great malaria epidemic occurred in 1896 at Merv concerning which a few details are available. It is stated(20) that in the summer of this year a peculiar kind of fever of a very virulent nature attacked the native inhabitants of the Merv oasis and the Russian garrison. In a great many of the Turkoman villages not a single person escaped it, and from the middle of March to the beginning of September (when the report was despatched by the *Times* Correspondent) 4,330 deaths had occurred out of the total population of 86,000, which is a mortality of 50 per 1,000 during six months.

The cause of the epidemic is supposed to have been the extraordinary overflow in the previous spring of the Murgab river and the effect of the subsequent excessive heat upon the inundated and sodden soil. A very similar occurrence has been reported from Persia, concerning which Lind, quoted by Deaderick,(8) gives a description which is worth reproducing. In an account of a trip up the Tigris in 1811 Lind states :—

" Here we were informed that the Arabs had broken down the banks of the river near Bassora, with a design to cover with water the deserts in its neighbourhood. This it seems is the usual method of revenge taken by the Arabs for any injury done them by the Turks in Bassora, and it was represented to us as an act of most shocking barbarity since

a general consuming sickness would undoubtedly be the consequence. This was the case fifteen years before when the Arabs by demolishing the banks of the river laid the environs of Bassora under water. The stagnating and putrid water in the adjacent country, and the great quantity of dead and corrupted fish at that time lying upon the shore, polluted the whole atmosphere and produced a putrid and mortal fever. Of this fever between 12,000 and 14,000 of the inhabitants died, at the same time not above two or three of the Europeans who were settled there escaped with life."

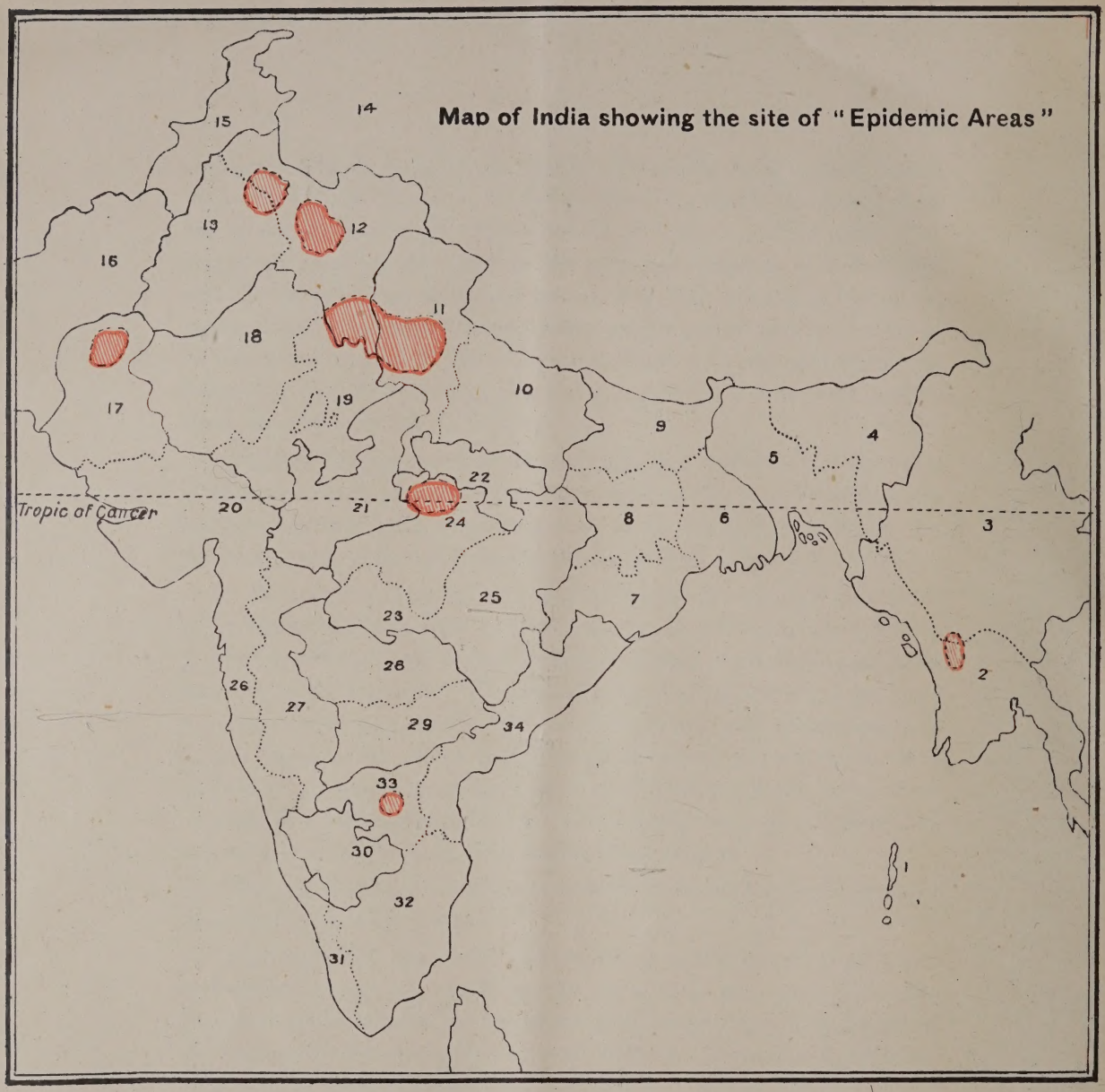
There is little room for doubt that these two epidemics are examples of true fulminant malaria. The Merv epidemic in particular presents features identical with those met with in the Punjab in 1908, as the following passage, quoted from the *British Medical Journal*(20), shows:—

" One reads of tents full of unburied corpses or untended sick, fields lying fallow and ownerless cattle wandering at will over the country. In Merv itself there was at first an uncontrollable panic which soon gave way to complete apathy. The whole business of the town and province has long been at a standstill. As even in ordinary years malaria prevails in this region to an extent that would be alarming anywhere else, it is clear that the excess must have been very great to create such a state of panic in a seasoned population. This year the sickness and mortality figures will probably be at least double if not tripled."

The distribution of fulminant malaria in India has been carefully investigated in recent years.

Christophers(1) has shown that portions of the sub-montane tract of the Punjab, are, *par excellence*, the site of these periodical epidemics. The chief epidemic area lies to the north of the province and comprises the districts of Gujrat, Gujranwala and Shahpur. The southern epidemic area includes the districts of Delhi, Gurgaon and parts of Rohtak—whilst smaller epidemic areas occur in the districts of Amritsar and Gurdaspur, and in the Ludhiana and Jullundur districts. Graham(21) states that the western half of the United Provinces was involved in the 1908 epidemic, the districts of Muttra, Bareilly, Moradabad, Budaon and Bulandshahr being chiefly affected. No previous epidemic has been recorded in these provinces. Fry(22) states that he can find no trace of fulminant malaria in Bengal in recent years, but a severe epidemic is reported to have occurred in the middle of the 19th century, apparently associated with the invasion of new areas. In the Rajshahi division of Bengal, Young(23) reported a series of extensive epidemics during the years 1905-1909,

MAP I.



NOTE.

The figures in Maps I and III refer to the civil divisions of India as given below

1. Bay Islands.
2. Lower Burma.
3. Upper Burma.
4. Assam.
5. Eastern Bengal.
6. Bengal.
7. Orissa.
8. Chota Nagpur.
9. Bihar.
10. United Provinces, East
11. United Provinces, West.
12. Punjab, East & North
13. Punjab Sout-Whest.
14. Kashmir.
15. N. W Frontier Provinces.
16. Baluchistan
17. Sind.
18. Rajputana, West
19. Rajputana, East.
20. Gujrat.
21. Central India, West.
22. Central India, East.
23. Berar.
24. Central Provinces, West.
25. Central Provinces, East
26. Konkan
27. Bombay, Deccan
28. Hyderabad, North.
29. Hyderabad, South.
30. Mysore
31. Malabar.
32. Madras, S E.
33. Madras, Deccan.
34. Madras Coast, N

but he was inclined to attribute them to epidemic malaria associated with the tropical aggregation of labour. Bentley,(5) as the result of his exhaustive investigations in Bombay City, arrived at the conclusion that whilst epidemics of malaria do occur in that city periodically he could find no trace of pandemic malaria as reported from the Punjab. Bentley therefore recognises that an extensive epidemic is not synonymous with fulminant malaria—a distinction the importance of which has already been emphasised.

Dyson(24) states that in the southern portion of the Bombay Presidency, including the highly malarious districts of Kanara, no evidence of epidemic malaria has been forthcoming, but in parts of the Deccan some evidence of modified epidemics has been obtained. In the Gujerat (Bombay) registration district the epidemic indices afford inconclusive evidence, whilst in Sind epidemic malaria comparable in type to that met with in the Punjab appears to occur.

In the Central Provinces Kenrick(25) states that " the epidemic of 1908 affected the northern districts of the Province on the border of the United Provinces and was obviously part of the pan-epidemic of that year." Stokes(26) in reference to the same epidemic says the districts affected were Saugor and Damoh, where the epidemic was, however, slight.

Justice(27) states that in Madras severe epidemic malaria is unknown. Horne(28) however has since found evidence of epidemic malaria in the Cuddapah district in the Madras Deccan.

Fulminant malaria has not been reported from Burma, but Williams (29) has recently published the results of an enquiry made into an outbreak of malaria in the Minbu district by Stewart and himself. He shows that over extensive areas of this district the malaria death-rates in November and December 1912 varied from 209 to 240 per mille. He adds : " There can, I think, be little doubt after a study of the mortality returns of the district for two years that the spread of malarial infection of a virulent type was directly associated with the extension of irrigation in the district. But it must be borne in mind that malaria was generally more rife in 1912 than in the previous year—and was the cause of a very high mortality in the neighbouring district of Thayetmyo, where there is no irrigation by canals, as well as in Mandalay and other irrigated districts."

The occurrence of fulminant malaria in India is, therefore, widespread. Its distribution is shown in Map I where the areas in which it is

believed to have occurred are shown in red. It will be observed that it is for the most part confined to the northern and central portion of the peninsula and that it is found chiefly to the north of the tropic of Cancer.

There are some apparent exceptions to this rule which will be referred to later.

Many parts of Ceylon are highly malarious and in 1895-1896 an epidemic of great malignity occurred in the districts of Galle and Matara. Clemow(14) states that this was clearly traced to soil disturbance and may therefore be considered to be an example of epidemics associated with the tropical aggregation of labour. In the Malay States malaria is rife and Malcolm Watson(30) described a severe epidemic at Klang and Port Swettenham in 1900 and 1901. The occurrence of this epidemic in two consecutive years together with the fact that it was associated with the tropical aggregation of labour, and ceased on the completion of the construction works and the dispersal of the staff, renders it certain that it was not an example of true fulminant malaria. Finally no evidence of the occurrence of these epidemics in Sumatra, Java, or Borneo has been obtained.

In North America malaria is prevalent chiefly in the south-east of the United States, but I have been unable to obtain any literature giving detailed observations in regard to the epidemiology of the disease in this country. Intense malaria is said to occur in parts of the valley of the Mississippi and its tributaries and Deaderick(8) mentions that epidemics have occurred as the result of this river overflowing its banks. In Massachusetts a severe epidemic occurred for the first time in 1885.

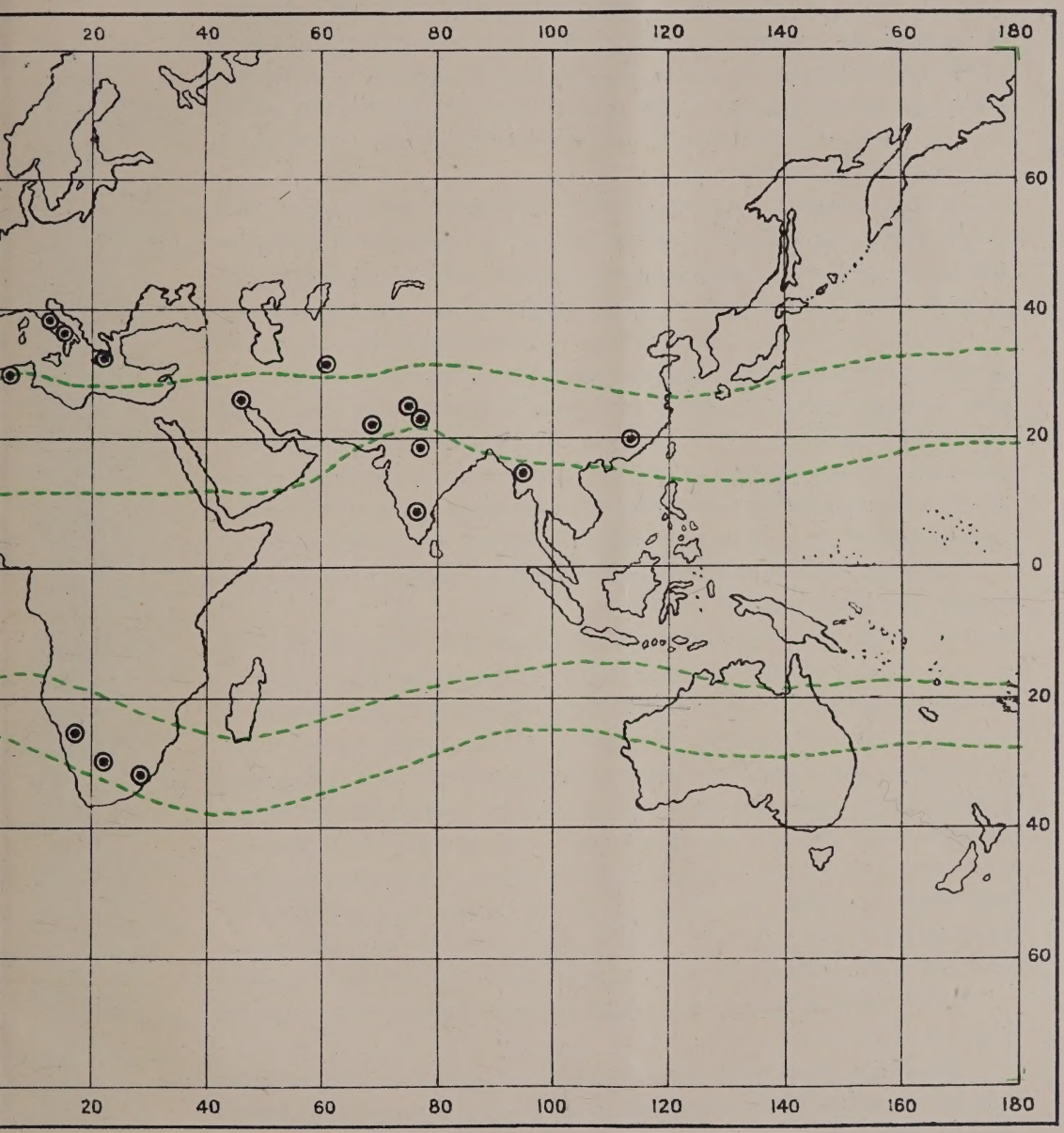
In the low coast region of Mexico, in Central America and in the Panama Canal Zone malaria of a virulent type is rife, but no epidemics appear to have been recorded in any of these regions. In the latter, as the result of the work of Gorgas and others, even the epidemics so commonly associated with the tropical aggregation labour have been mitigated or prevented.

In South America malaria is severe throughout the tropical zone, especially in the riverains of the Orinoco and the Amazon, but whilst no epidemics appear to have been recorded detailed information is lacking. In Bolivia and Paraguay malaria is less severe, but Mannaberg states that regions in Bolivia, Paraguay and Uraguay are greatly *and sometimes intensely infected.*

In the Argentine Republic malaria is almost absent. In Australasia and Oceania malaria is not a formidable disease. In Australia itself

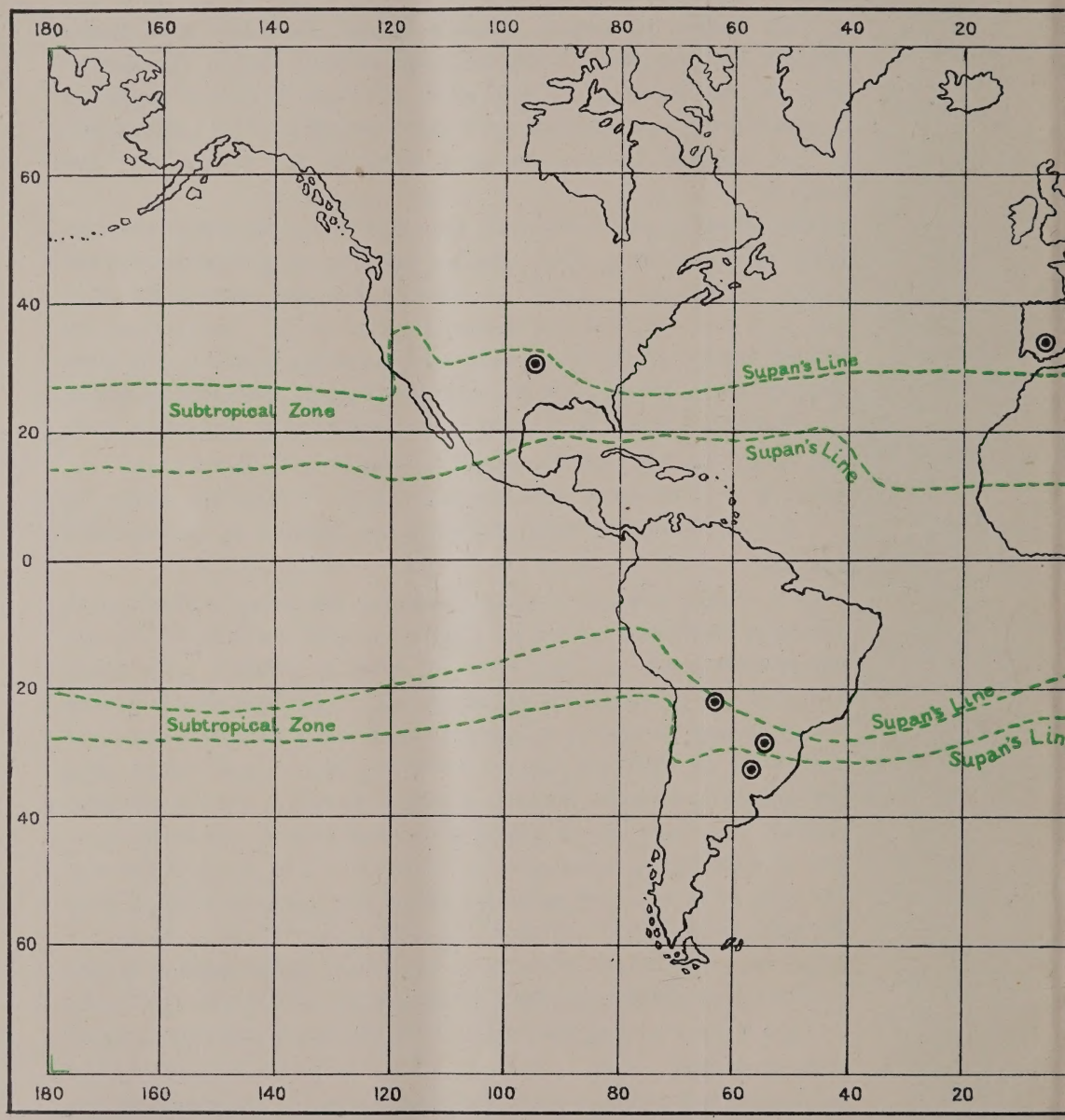
II.

wing the Distribution of Fulminant Malaria.



MA

Map of the World on Mercator's Projection s



it only occurs in the extreme north and along portions of the east coast. In New Zealand malaria is said to be entirely absent, and in none of these regions has any evidence been found pointing to the occurrence of fulminant malaria.

From this review of the history and geography of fulminant malaria certain salient features emerge. In the first place, it is seen that whilst fulminant malaria only occurs in endemic areas of the disease, it does not occur in all paludic countries, nor even in parts of the world such as the West Coast of Africa where the disease is notoriously most virulent and widespread. Furthermore, it appears to occur chiefly in the sub-tropical zone and to be absent from those parts of the world where the climate throughout the year is strictly tropical. Certain apparent exceptions to this rule will be considered later. The above facts are illustrated in Map II in which the areas where fulminant epidemics are believed to occur are shown in red. The boundaries of the sub-tropical zone are indicated by means of Supan's lines which represent isotherms of 68°F. (20°C.) for the temperature of the coldest month and the same isotherm for the mean temperature of the year.

It is not possible to show accurately the position of the fulminant areas in the map which thus merely serves to indicate the region of the world in which they are located in reference to Supan's lines.

A scrutiny of Map II in addition to showing the distribution of these epidemics also discloses the fact that many of the areas subject to fulminant malaria in the sub-tropical zone are in the centre of land areas which, it may be inferred, possess a "continental" rather than an "insular" climate. Further, no trace of fulminant malaria has been discovered in any small island with the exception of Mauritius where the climate tends to be more equable than that of inland areas in the same latitude.

In addition to the fulminant areas in the sub-tropical zone evidence has been deduced to show that areas such as Italy and Greece may be also involved, so that whilst it may be stated that fulminant malaria does not occur in the essentially tropical part of the tropics, it may prevail in certain portions of the temperate zone where malaria is endemic.

Another point which a review of the literature brings out is the marked association of fulminant malaria with the overflow of rivers. The Mississippi, the Orange river, the Tigris, the Murgab, the Indus and

its tributaries and the Yangste Kiang are all prominently mentioned in this connexion.

Again it will be noted that whenever the period of the year in which these epidemics occur is recorded, the autumn is invariably mentioned as the time of the year in which they prevailed. In this connexion it is particularly interesting to find that in the southern hemisphere, where the seasons are reversed, it is still in the autumn that fulminant epidemics occur.

Finally something must be said in regard to the exact *site* of fulminant epidemics within these areas where they are apt to occur. In this connexion it must suffice to refer to the " epidemic areas " in the Punjab of which alone there is any certain knowledge. Christophers shows that they are situated in certain portions of the submontane tract, more especially in the neighbourhood of the large rivers or along the line of old river-beds. No fulminant epidemic has been discovered, on the one hand, in the sandy waterless tract on the west of the provinces or, on the other, in the highly malarious tract at the foot of the Himalayas or in the broken country intervening between the hills and the plains. Map I shows the location of the areas subject to intense epidemic conditions.

The site of selection of a fulminant epidemic in the Punjab is then, certain portions of the submontane plains which are subject to inundation by means of the overflow of rivers or of mountain torrents.

IV.—The Temperature Factor in Malaria.

In view of the peculiar distribution of fulminant malaria it is necessary to examine more closely the effect of climate, and more particularly the effect of temperature on malaria. It is not possible to study the climatic conditions of all the areas in which it is believed that fulminant malaria occurs, so reference will only be made to the climatic circumstances of that portion of Northern India known as the Punjab.

Without going, for the present, into more precise details, it may be said that in the Punjab two well marked seasons occur—a summer or " hot weather " and a winter or " cold weather," which succeed one another with considerable abruptness, so that spring and autumn are both short and ill-defined. In the cold weather which roughly lasts from November to March—somewhat more in the north and somewhat less

in the south—the climate is cold and the rainfall scanty. During a considerable portion of this period the maximum daily temperature remains below 70°F. and the minimum between 50°-40°F. and occasionally lower. The climate of the Punjab in the winter thus approximates to that of many countries in the temperate zone. Towards the end of April the hot weather sets in rapidly and the shade temperature mounts up through the eighties to the nineties. In June temperatures of 110°-120°F. are not uncommon, and until about the second or third week in the month, when the monsoon usually " breaks," the atmosphere is dry. With the onset of the rainy season which usually lasts throughout July, August and September, there is a slight fall in the shade temperature, but a considerable increase in the atmospheric humidity due to evaporation from the numerous pools and sheets of water formed as the result of the copious but intermittent rainfall.

During this period of about three months the Punjab climate closely resembles that of a tropical country. Towards the beginning of October a drop in a night temperature begins to be noticeable, thereafter the shade temperature in the day also decreases, so that by the end of the month the cold weather has become almost completely established.

These climatic changes must exercise a considerable influence on all forms of animal life, for it is obvious that the more strictly tropical fauna will be subjected to an unfavourable environment during the rigorous cold weather of the Punjab.

It now becomes necessary to consider in more detail the effect of these climatic changes on malaria parasites and on their definitive host the mosquito.

(*A*).—*The Effect on the Malaria Parasite.*

In regard to the effect of climatic changes on malarial parasites circulating in the blood of man there is unfortunately no means of judging. It is well known that great heat and cold—" chills "—favour the onset of relapses, but it is probable that they exercise their influence, in part if not entirely, by their depressing effect on the human host. All that can be said under this head for the present is that in so far as malaria in the Punjab is due to the sub-tertian or tropical parasite, the latter must encounter conditions in the Punjab not usually met with in the regions of its greatest prevalence, that is to say in the tropics.

This point will receive further consideration when the parasitology of fulminant malaria is considered.

(B).—The Effect on Anophelines.

Numerous observations have shown that with the onset of the cold weather mosquitos rapidly decrease in numbers. From December to February imagines are difficult to find and larvæ are distinctly scarce. This is more marked in the north of the province than in the south, for instance, a search extending over a week in the month of January in a town in the north of the province failed to reveal a single anopheline larva or adult.

It is the common experience during this period that mosquitos rarely bite and the use of mosquito nets is everywhere discontinued, but in order to determine the actual temperature at which anophelines cease to bite, some experiments were carried out with *A. rossi*, and *A. fuliginosus* together with *Culex fatigans*.

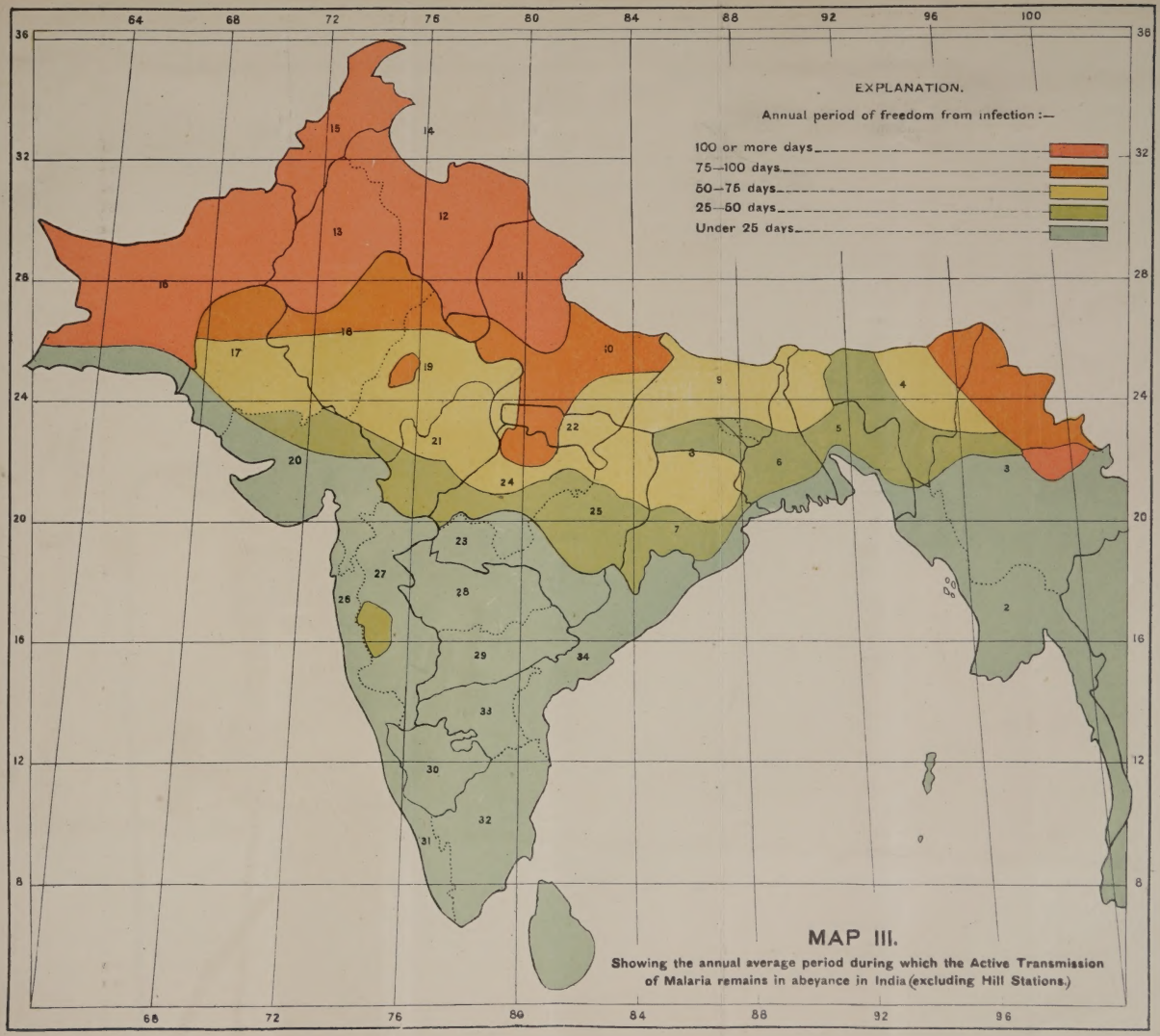
These experiments, the details of which need not be given here as it is proposed to repeat and extend them when opportunity offers, appeared to show that whilst *Culex fatigans* would not bite freely at temperatures lower than 78°F., both *A. rossi* and *A. fuliginosus* were active and bit freely at temperatures as low as 54°F.

It has, however, been shown repeatedly by Jansco (31) and others that cessation of development of zygotes in the midgut of the mosquito takes place when the atmospheric temperature remains below 60°F.

In view of this fact, together with the undoubted scarcity of anophelines and the rarity with which they bite during the "cold weather," there is ample ground for stating that *for a portion of each year in the Punjab malarial infections do not take place.*

In order to measure more accurately the duration of the infection free period, which varies even in different parts of the Punjab, the number of days at which the shade temperature at 8 A.M. did not reach 60°F. has been calculated from the Daily Weather Reports(32) for 1911 and 1912 kindly supplied at the instance of Dr. Gilbert Walker, Director-General of Observatories in India.

This temperature has been selected, after considerable deliberation, as being approximately the temperature below which infection and re-infection of man by anophelines ceases, for it may be remarked that when the 8 A.M. temperature fails to reach 60°F., the temperature for the greater portion of the preceding night has been considerably below that figure. In any case this temperature is only to be regarded as an index and it will not invalidate the argument if further investigation should prove that a more accurate figure might have been chosen.



MAP III.

Showing the annual average period during which the Active Transmission of Malaria remains in abeyance in India (excluding Hill Stations.)

In Table A is given the average number of days for the years 1911 and 1912 in which the 8 A.M. temperature, in the Punjab and the United Provinces, failed to reach 60°F.

TABLE A.

	United Provinces.	Average No. of days 8 a.m. temperature below 60°F.		Punjab.	Average No. of days 8 a.m. temperature below 60°F.
U. P. East	1 Gorakhpur	81	South	1 Delhi	98
,,	2 Benares	60	,,	2 Sirsa	107
,,	3 Allahabad	69	,,	3 Ludhiana	121
,,	4 Lucknow	79			
,,	5 Bahraich	87		Average	108·6 days
,,	6 Cawnpore	84			
	Average	76·6 days	Centre	4 Montgomery	114
			,,	5 Ambala	123
			,,	6 Lahore	130
West	7 Bareilly	100	,,	7 Multan	100
,,	8 Mainpuri	100			
				Average	116·7 days
,,	9 Roorkee	116			
,,	10 Agra	80	North	8 Khushab	114
,,	11 Jhansi	69	,,	9 Sialkote	129
			,,	10 Rawal Pindi	142
	Average	93 days		Average	128·3 days

In Map III, the result of calculating the same figures for the whole of India excluding Hill Stations are recorded pictorially according to the following plan. Areas in which the 8 A.M. temperature failed to reach 60°F., on 100 or more successive days are coloured red, brown is used where this period was over 75 and less than 100, yellow for periods of 50 to 75 days, green for periods of 25 to 50 and blue in areas where the number of days was less than 25.

A scrutiny of this map brings out clearly the fact that in contrast with the condition of affairs in the tropical part of India, there occurs in Northern India a period each year, which varies according to the latitude, altitude and proximity to the sea, during which malaria infection must almost, if not absolutely, cease. Indeed, it seems clear that in parts of the Punjab malaria infection cannot be contracted during as much as one-third of the year.

It is now necessary to consider briefly the effect on man of this period of freedom from infection. Daniels(33) states—and it is a well-known fact—that simple tertian infections disappear in England without treatment in about three years, and malignant or sub-tertian infections in

about two years. Sir Ronald Ross(6) without attempting to differentiate between the species of parasites, suggests a "reduction factor" of 50 per cent. in three months, that is to say, in three months 1,000 cases of malaria would be reduced to 500 by spontaneous cure. In these circumstances an "interruption" of infection, especially when prolonged for periods of 100 days or more, involves not only an absence of reinfection but also a considerable reduction in the amount of residual infection.

The subject of reinfections in malaria begins, therefore, to assume a new importance, more especially since it has been shown that fulminant malaria is almost exclusively restricted to areas in which interruption of infection over a considerable period must frequently occur.

That some connexion exists between these two circumstances receives support from the following facts. Christophers(1) remarks that, in the 1908 epidemic, the eastern half of the United Provinces showed no evidence of a fulminant outbreak in spite of the fact that its rainfall was excessive and exceeded in amount that experienced in the western half, where the epidemic was severely felt.

From Table A, it is seen that the average number of days of freedom from infection in the western portion is greater than in the eastern half, the average for the former being 93 days as compared with 76·6 days in the latter. The meteorological stations in the vicinity of the epidemic area in the United Provinces are Bareilly and Mainpuri where the average number of days of freedom from infection is somewhat higher—*viz.*, 100 days.

On examining Map III carefully, it is seen that the only portion of the United Provinces which has been visited by a fulminant epidemic is almost exactly the area in which the average annual number of days of freedom from infection reaches 100. In this respect, therefore, it more closely corresponds to the Punjab than to the rest of the United Provinces.

Again, Christophers has shown that in the Punjab, tracts in the north of the province, where the average annual duration of the infection-free period is 128·3 days, are most prone to suffer from fulminant epidemics; areas in the centre come next (average days of freedom from infection 116·7) and the southern area, where the average annual duration of freedom from infection is 108·6 days, are least subject to these outbreaks.

Finally, Graham(21) states that the 1908 epidemic in the United Province is unique in the malarial history of that Province.

The frequency distribution of major fulminant epidemics, as given by Christophers and Graham, together with the average number of days of freedom from infection in each area, is given in Table B.

TABLE B.

To show the frequency distribution of fulminant epidemics.

Epidemic Area.	Average number of days of freedom from infection.	Number of recorded fulminant epidemics.
1. Western United Provinces ..	100	one
2. South Punjab ..	108·6	two
3. Central Punjab ..	116·7	three
4. North Punjab ..	128·3	four

Evidence of epidemic malaria though apparently of a mild nature has also been discovered in the districts of Agra in the United Provinces, in parts of Sind and in the two mostly northerly districts of the Central Provinces.

It will be noted that the areas covered by these epidemics all appear brown in Map III, signifying that their annual period of freedom from infection exceeds 75 days. In regard to the mild epidemics reported from Bombay and Madras the map shows that the period of interruption of infection does *not* exceed 25 days in any part of these Presidencies except near Poona.

The epidemic areas however are located in the Deccan which is a tableland situated from 3,000—6,000 or more feet above sea-level. The only locality on this plateau which has been shown definitely to have suffered from a fulminant epidemic, is the Cuddapah district in the Deccan.

It so happens that Cuddapah town, the headquarters of the district of the same name, possesses a meteorological station, but its temperature records show that the period of "interruption of infection" to be nil. On consulting the Imperial Gazetteer of India,(34) however, it is found that whilst the district stands at a height of 1,500—2,250 feet above sea-level, the town itself is situated in an enclosed valley only 500 feet above sea-level. The Gazetteer states that a very marked contrast exists between the climate of the town and the district and that whereas the former is the "hottest place in the whole presidency," the upland part of the

district is exceptionally healthy and bracing. It is in the latter area, which Horne describes as being " a dry, barren area possessing a rainfall which is usually scanty, but when heavy liable to cause floods," that the epidemic occurred.

In reference to the Burma epidemic, in the absence of precise knowledge regarding local conditions, no opinion can be given in regard to its nature.

To sum up, it would appear that, not only is there some reason to believe " interruption " of infection is one factor in these outbreaks, but the facts also lend themselves to the suggestion that, other circumstances being favourable, the longer the period of " interruption" in any area, the more liable such an area becomes to these epidemics. Secondly, there appears to be a gradual decrease in the intensity of fulminant malaria as we pass from the north to the south of India, so that it seems probable that epidemics of every degree of severity may be met with according to local climatic conditions. Thirdly, the remarks in regard to the epidemic reported from the Deccan suggest that before the occurrence of a fulminant epidemic can be excluded in the tropics the climatic circumstances, not of the nearest meteorological station, but of the exact locality involved, must be studied. Finally, the inference may be drawn from this study of the relationship of climate to fulminant malaria that the latter may be expected to occur in certain areas which a knowledge of local conditions will readily enable one to pick out.

V.—The Nature of Malarial Immunity.

Kelsch and Kiener(35) and others have pointed out that complete immunity to malaria—that is absolute resistance to infection—rarely if ever occurs. These authors, therefore, prefer the term " relative tolerance " as being a more appropriate and accurate description of the immunity conferred by malarial infection.

It is true that Celli,(2) Marchiafava and Bignami(36) and others have recorded cases of complete natural immunity, congenital immunity and even family immunity, but the rarity of these conditions renders them of little value except as clinical curiosities.

On the other hand, most authorities are agreed that such immunity to malaria as occurs is usually a partial immunity acquired by residence in endemic areas.

Racial immunity is generally supposed to exist, and the Caucasian race is usually said to be more susceptible to malaria than the Ethiopian

race, but there is no general agreement on this point. At one time it was held by Koch and others that the black races in Africa possessed an almost complete immunity, but further investigation has proved the incorrectness of this view, and it is now well-known that they suffer from this disease, although not to the same extent as the white races living alongside them. Thus Plehn(37) states that the inhabitants of the Kamerun Coast seldom suffer from fever, and when they do the febrile paroxysms rarely last more than a few hours. He states, however, that a change of residence deprives them of this relative immunity at least temporarily. Moreover, although hæmoglobinuria prevails in a very grave form amongst Europeans in Kamerun, he did not see a single case amongst 276 cases of fever observed by him in Negroes. Facts of a similar nature have also been recorded by other observers.

A study of the literature of malaria shows a wide divergence of views in regard to the nature of malarial immunity.

Craig(9) states that the following rules governing malarial immunity may be said to be "fairly well proven" by the observations of many observers :—

(1) In severely infected regions, provided conditions are favourable for infection, a relative immunity is generally observed in the adult population and is more promptly acquired as more reinfections occur in childhood.

(2) In slightly infected regions a relative immunity is not rapidly acquired; fewer children are infected and reinfections are less common.

(3) In countries in which seasons such as winter occur, which are unfavourable to malaria, an acquired immunity is rarely observed as reinfections are rendered less numerous.

The facts on which these conclusions are based are, however, not fully stated and in the next paragraph Craig adds that in some regions the above rules do not hold good.

From his consideration of this subject Sir Ronald Ross(6) draws an important deduction. He states that where there is much malaria so many of the native adults will be immune that few of them will show signs of infection, and conversely where the adults are frequently attacked, the amount of malaria should be comparatively slight.

Smith, quoted by Deaderick,(8) states that whilst the natives of Sierra Leone are infrequently attacked, and then only with mild degrees

of malaria, a West Indian regiment of Negroes stationed at Sierra Leone suffered very severely with attacks, many of which proved fatal.

In view of these and many other similar statements to be found in the literature of malaria, it is difficult to avoid the conclusion that even racial immunity is for the most part an acquired immunity, which requires for its maintenance constant residence in an endemic area.

In these circumstances it is clear that one infection with malaria confers little or no immunity, for in no other way is it possible to explain the fact, so often noted, that constant residence in an endemic area is essential to the maintenance of even a relative protection. That spontaneous recovery from a single infection is not the result of the development of a high degree of immunity is suggested by the fact that, although the " life " of a single infection is not more than two or three years, a high death-rate from malaria is maintained up to eight or ten years of age. Finally, there is the fact that immunity becomes decreased or lost by residence in non-endemic areas. The conclusion therefore is irresistible, that repeated reinfection is an important factor in the production and maintenance of malarial immunity.

In regard to the mechanism of malarial immunity little is known. It follows, however, as a logical conclusion from what has been said above, that the elaboration of protective substances on which all forms of immunity are believed to depend must be chiefly ascribed, in the case of malaria, to *recent* infection. And since Ehrlich(38) has shown that the destruction of parasitic protozoa produces anti-bodies " fairly rapidly, " it may be surmised that malarial parasites are destroyed in relatively greater numbers in fresh as compared with old infections.

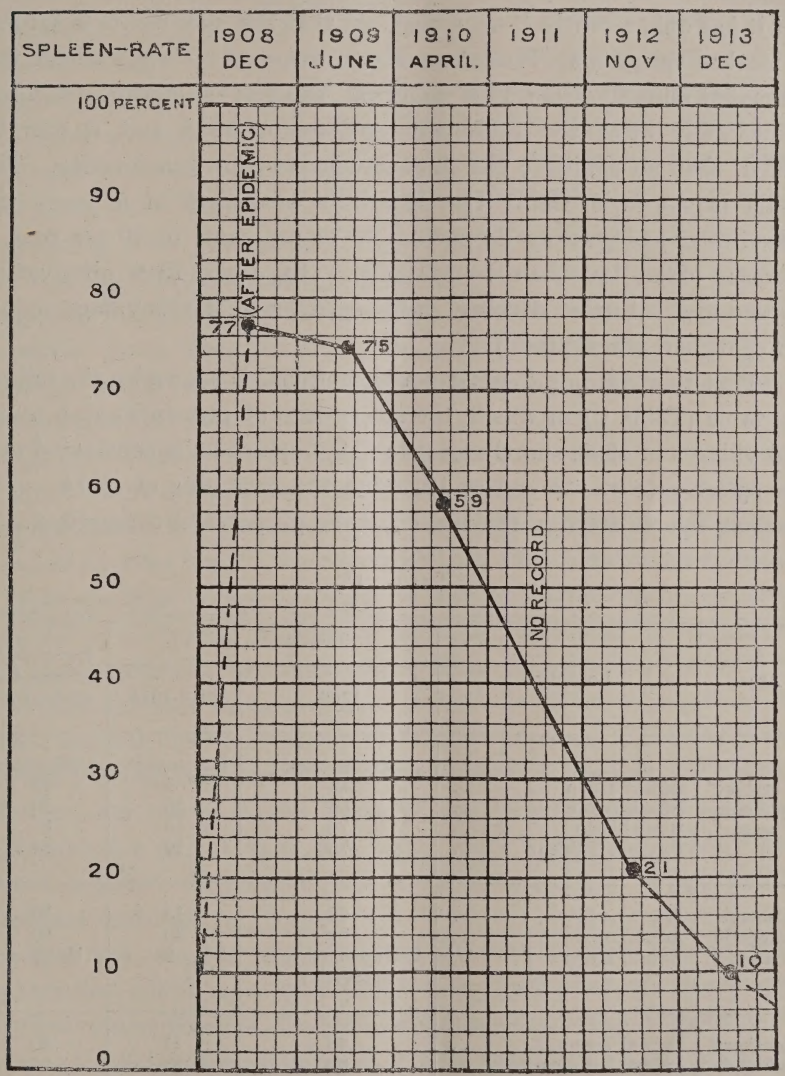
But whether these theoretical considerations be correct or not, the importance of reinfection has been clearly and definitely established.

Many problems in connexion with malarial immunity would be solved if it were possible to measure directly the degree of immunity possessed by man. Unfortunately this is at present impossible, but it is believed that the spleen-rate can be utilised to furnish an index of the degree of immunity possessed by a community. A few paroxysms of ague do not usually produce chronic splenomegaly and it is extremely doubtful if a single untreated infection ever does so. Splenic enlargement is usually the result of a summation of infections and, this being the case, it affords a rough index of the amount of *reinfection* that is taking place. But reasons have just been deduced which suggest that the immunity of a community also depends on the amount of reinfection.

Hence the spleen-rate, indirectly, gives a rough index of the degree of immunity possessed by a community. This, it is true, cannot be estimated but if the spleen-rate remains fairly constant in any given community it

CHART II.

Spleen-rate of Kathala, Gujrat District, Punjab.



may be assumed that the immunity of that community likewise remains constant; on the other hand, if the spleen-rate shows marked fluctuations over a period of years it will likewise be associated with a fluctuating

immunity. It is, therefore, necessary to know if variations in the spleen-rate occur in the sub-tropical zone where interruption of infection is apt to occur. In this connexion it is only possible to refer to that portion of this zone which embraces the Punjab.

Unfortunately up to the present no systematic records of spleen-rates have been taken periodically, as not only was their value unknown, but it has only recently been recognised that the spleen-rate is subject to marked variations. The spleen-rate, however, of a certain village was estimated annually from 1908 to 1913. The first estimation was made immediately after the fulminant epidemic of 1908 and, it may be added, that no epidemic has since taken place in this locality. The result is shown in Chart II. It will be seen that in 5 years the spleen-rate* has steadily dropped from 77 per cent. to 10 per cent. a decrease of no less than 78 per cent. (In June 1914 observation showed that a further decrease in the spleen-rate of this village to 1·4 per cent. had taken place.)

That this state of affairs is not exceptional is shown by the following table (Table C) in which the spleen-rate of certain Punjab towns and villages in 1909, shortly after the 1908 epidemic, is contrasted with the spleen-rate at the end of 1913 and the beginning of 1914. The Kathala figures are again included for the purposes of comparison.

TABLE C.

Area.	Locality.	Spleen-rate.		Percentage reduction in spleen-rate.
		1909.	1913-1914.	
		Percentage	Percentage	Percentage
Northern epidemic area.	Gujrat Town ..	43	3	93
	Bhera Town ..	84	25	70
	Miani Town ..	79	15	81
	Kathala Village ..	75	10	84
Central epidemic area.	Amritsar City ..	63	15	76
	Atari Town ..	81	30	60
	Batala Town ..	Unknown (severe epidemic)	2	Unknown
Southern epidemic area.	Palwal Town ..	88	17	80
	Palwal Villages ..	82	17	79
	Hodel Town ..	57	15	74

* *Note.*—In order to avoid encumbering the text the figures on which all spleen-rates have been determined have been relegated to the Appendix attached to this paper.

Chart II shows that the decrease in the spleen-rate is gradual during the first two years after the epidemic, thereafter it becomes somewhat more rapid, so that a reduction of 87 per cent. has been affected in five years. In the light of what has gone before it follows that a great diminution in immunity has also taken place during this time, and using the spleen-rate as an index of immunity it may be said that the immunity has undergone a reduction of 87 per cent. of its amount in 1908. If the above assumption be correct, it follows that fulminant epidemics are extremely unlikely to occur in the same locality in consecutive years. This point now demands consideration. Chart I shows that major epidemics occurred in the years 1876, 1878, 1879, 1884, 1890, 1892, 1900 and 1908. Except for the epidemics in the first three years and those in the years 1890 and 1892 a period of not less than 5 years has intervened between consecutive epidemics. In regard to the apparent exceptions it is found that *the same area* has never been involved in two successive years and that whilst the period intervening between two epidemics in the same area may vary between 4 and 29 years, the most common period is six years.

In this connexion Celli states: "From time to time in the various localities where malaria is endemic the disease becomes epidemic and even pandemic, this occasionally occurs in places *where it had not been prevalent for some time.*" He also adds that the mortality from malaria in "Italy has been subject to regular periodic oscillations with a *maximum every five or six years.*" The italics are mine. Assuming for the moment that these epidemics are associated with a temporary increase in the amount of infection being combined with a low degree of immunity, the reason for their cyclical occurrence becomes apparent. Excessive rainfall and flooding may in any year bring about a temporary increase in infection, but owing to the fact that the immunity conferred by one epidemic takes some four or five years before it becomes greatly diminished, a period of at least equal duration must elapse before another fulminant outbreak can occur.

It is now possible to understand the fact pointed out by Christophers that whilst most epidemic years in the Punjab are also years of very heavy precipitation, the heaviest monsoon rain may be unassociated with any fulminant epidemic. It is also possible to comprehend the significance of an observation made by Major Perry,(48) who found that in the case of Kathala (Chart II) and neighbouring villages the autumn of 1909 did not differ markedly from the preceding autumn in

respect of the factors favouring epidemic malaria. Thus, in both years the parasite rate in children was extremely high, anophelines were very prevalent, rains were abundant and local flooding was severe! Yet the autumn of 1908 was marked by a severe fulminant epidemic whilst the following autumn was remarkably free from malaria.

The part played by malarial immunity is therefore one of great importance and wide application. In those parts of the tropics where infection may be contracted throughout the year the immunity of the community ordinarily remains constant in response to an approximately constant amount of reinfection. In such a community, it may be affirmed, even if the spleen-rate be high, the death-rate due *directly* to malaria will be low because the amount of infection is counterbalanced by an almost equivalent degree of immunity. In these circumstances the rarity of pernicious malaria (and blackwater fever) *amongst the indigenous inhabitants* and the absence of fulminant epidemics in the strictly tropical part of the tropics is rendered easy of comprehension. On the other hand, in the sub-tropical and temperate zones the amount of infection, and thus the degree of immunity, of a community may be subject to great fluctuations, and when a period of low immunity is associated with a sudden great increase in the amount of infection, the unprotected population will suffer from a severe epidemic. It is thus clear that a spleen-rate of 5 per cent. may have a different significance in the tropics and in the sub-tropics. In the former it merely signifies a low degree of endemic malaria; in the latter it may mean that a fulminant epidemic will occur at the first favourable opportunity.

Finally, it is possible to draw the important inference that fulminant malaria may be expected to occur only in areas where fluctuations in the spleen-rate, over a number of years, are marked. From this it follows that a new importance is to be attached to the spleen-rate in the measurement of malaria; for in addition to the valuable information it already yields, its periodical estimation may bring to light facts of great importance.

VI.—The Parasitology of Fulminant Malaria.

In the account of the geography of fulminant malaria given in Part II, mention is made of the fact that these epidemics usually exhibit an autumnal periodicity. It will also be recollected that two fulminant

epidemics in S. Africa were recorded as having commenced in January and to have reached their maximum in the following months, the latter period being the autumn in the Southern Hemisphere.

In Italy Celli(3) states that it is only in the south of Italy that the mortality from malaria exhibits periodic oscillations, and he further shows that it is only in southern Italy that the æstivo-autumnal parasite exhibits a marked degree of prevalence.

In the Punjab the researches of Christophers have shown that fulminant malaria is strictly an autumnal manifestation: he indeed uses the October and November deaths in order to measure the intensity of these epidemics. There is, however, no direct evidence available as to the relative prevalence of malaria parasites at the time of the 1908 Punjab epidemic, for Christophers did not commence his researches until the following spring. It is true that he, at this time, found in the areas which he examined a predominance of benign tertian infections, but in view of the fact that the writer(39) has shown that benign and sub-tertian parasites in Northern India exhibit well marked seasonal variations and that, whereas benign infections are largely spring infections and sub-tertian infections are chiefly confined to the autumn, observations made in the spring are inconclusive. The attached chart (Chart III) extracted from the writer's paper shows the monthly incidence of benign and sub-tertian infection in prisoners in the Lahore Central Jail. It should be added that the observation was made during a normal year so far as malaria epidemics are concerned.

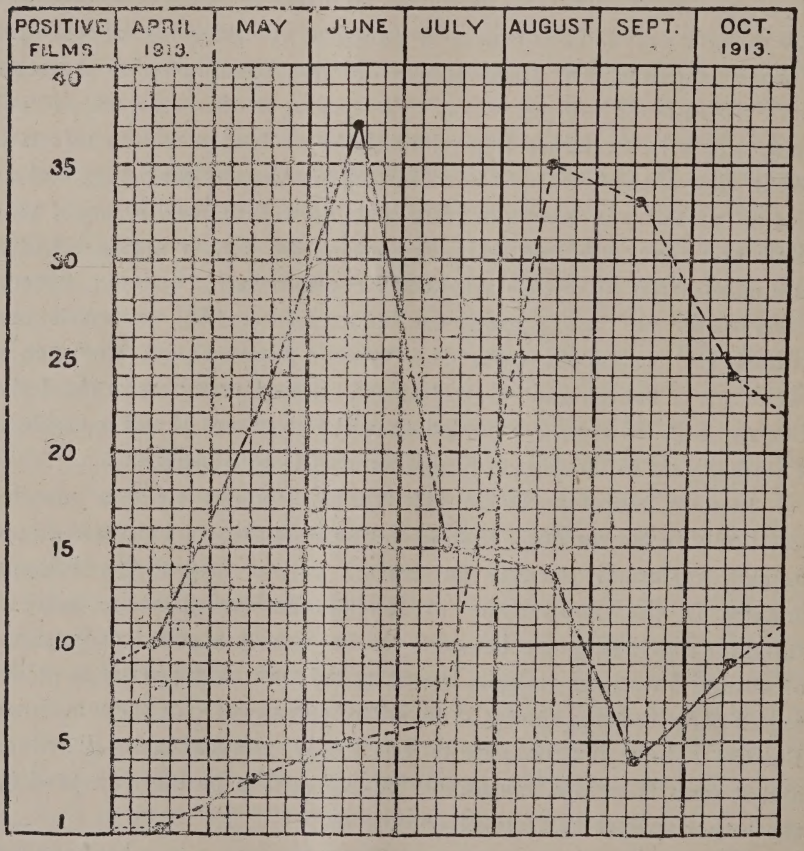
In view, therefore, of the fact that fulminant malaria manifests itself only in the autumn, that so far as is at present known the predominant autumnal parasite in certain areas subject to fulminant malaria is the sub-tertian or æstivo-autumnal parasite, and that fulminant epidemics are believed to be merely marked exaggerations of normal autumnal malaria, strong *primâ facie* evidence exists pointing to this parasite being chiefly, if not entirely, concerned in these outbreaks. But the sub-tertian parasite is essentially tropical in its distribution and it may, therefore, reasonably be expected to be more adapted than the other species to tropical conditions.

This conclusion receives support from the fact, which has been noted by Christophers(40) and others, that the malignant tertian parasite produces gametes more profusely and for a longer period of time than other species, thus suggesting that it is particularly adapted to propagation at short intervals. In the sub-tropical zone this condition cannot

always be fulfilled, with the result that abnormal conditions may bring about abnormal results in the shape of a fulminant epidemic. In this manner it is thought may be explained the circumstance, demonstrated in Map II, that the main epidemic areas are located not in the tropics

CHART III.

Showing the prevalence by months of malaria parasites in prisoners in the Lahore Central Jail.



themselves, but in a comparatively narrow strip of territory intervening between the tropical and temperate zones.

There is, therefore, a considerable amount of evidence to connect the *tropical* or malignant tertian parasite with fulminant malaria.

VII.—The Mechanism of Tropical Malaria.

It is now possible to understand and explain many obscure points in the endemiology and epidemiology of the disease. It has been found necessary to divide malaria from the epidemiological point of view into various sub-heads, and it is now proposed to describe each in turn in the light of the facts elucidated above. An important principle underlying the protean nature of malarial manifestations has been shown to be closely related to the subject of immunity.

In connexion with tropical malaria as defined at the commencement of this paper, little more need be said. Here infection is of almost perennial occurrence with the result that a more or less complete permanent equilibrium is established between the amount of infection and the degree of immunity. In these circumstances the spleen-rate (and the immunity) remain fairly constant and the former merely serves to afford an index of the local prevalence of the disease. It may be said that new comers—that is the young children—in tropical countries whose immunity at birth may be presumed to be nil, ought, on this theory, especially in highly endemic areas, to be decimated to such an extent that the population would be quickly wiped out. This is not necessarily the case, for it is part of the argument that infection commences shortly after birth and that it is continuous. On the other hand, the children in sub-tropical zones may live months or even years before they become subjected to a heavy dose of infection.

It is true that in the tropics a high spleen-rate is frequently accompanied by a high mortality, but this is an indirect result, due not to the severity of the disease, but to malarial cachexia and general debility paving the way for many intercurrent diseases.

There is a striking analogy between the confirmed opium-eater and the malarial cachectic. Both have purchased their immunity at a heavy price. In the former the emaciated frame, sallow complexion and other signs of debility proclaim the victim of a drug habit; in the latter the enlarged spleen, the lack of physical and mental energy and the shrunken body bear witness to the havoc wrought by long standing malaria. In the case of neither does death often take place as the direct effect of their respective poisons, but both readily fall victims to intercurrent affections.

Conversely, the victims of fulminant malaria and acute opium poisoning are in much the same position; both may readily succumb to

doses which would prove comparatively harmless to the individual long habituated to these poisons.

It has been stated that a more or less constant spleen-rate is characteristic of tropical malaria, but this must not be taken to mean that no variations in the spleen-rate ever occur. It is obvious that when malaria invades new localities a rising spleen-rate will shortly be witnessed. In such a case a fulminant epidemic might easily occur and, indeed, it has been mentioned that a severe epidemic took place in Mauritius shortly after the disease was introduced into that island. Again owing to natural causes (or by artificial means, such as anti-malarial measures) the amount of malaria may become permanently decreased in a tropical community with the result that the spleen-rate will permanently fall. In this case, however, no fulminant epidemic can occur because, although the immunity will be decreased, the amount of reinfection will be correspondingly diminished and "equilibrium" will thus be maintained.

Tropical malaria, then, is ordinarily associated with a deterioration of health proportionate to the local prevalence of the disease, but not with the occurrence *amongst the indigenous inhabitants* of the graver forms of malaria or of fulminant epidemics.

VIII.—The Mechanism of Sub-tropical Malaria.

Although fulminant malaria only constitutes one manifestation of malaria in the sub-tropical zone, it nevertheless constitutes so alarming a feature as to demand very special consideration.

Its mechanism has, however, already been sufficiently indicated and it only remains to add that, according to my conception, true fulminant epidemics occur only in areas where, owing to climatic reasons, infection cannot take place throughout a considerable period of each year; that during this period, as the result of the cessation of infection, there is a decrease in immunity which in the course of a few years may become considerable. If in these circumstances conditions suddenly become unusually favourable to the parasite, the lack of equilibrium between the degree of immunity and the amount of infection, enables a fulminant epidemic attended by a high mortality, more especially amongst children, to occur.

It must, however, be emphasised that in the light of the part played by immunity in these epidemics their restriction to the sub-tropical zone is merely, as it were, an accidental result of climatic conditions. For example, if it were possible to place all the inhabitants of one-half of

Bombay city under mosquito curtains for five years a fulminant epidemic might be anticipated to follow their removal, provided the other factors remained constant in the meantime. Again, the European on the West Coast of Africa who is prostrated by malaria, or the military expedition composed of European troops which is decimated by the disease during operations in a tropical country, are equally victims of fulminant malaria. It is, however, convenient to restrict the use of this term to extensive epidemics produced as the result of climatic circumstances interfering with the normal mechanism by means of which "equilibrium" is maintained between the amount of infection and the degree of immunity.

But a decrease in immunity will not of itself suffice to produce a fulminant epidemic unless the amount of infection is also increased. In sub-tropical climates there is necessarily some oscillation in the amount of seasonal infection, but the restriction of the site of these epidemics within this zone suggests that this normal fluctuation in the seasonal incidence of infection is not itself sufficient to produce an epidemic. Other factors favourable to the malarial parasite must be at work.

One of these favourable conditions Christophers(1) has shown to be (and the study of the geography of fulminant epidemics has emphasised this point) the occurrence of "flooding" either as the result of excessive rainfall or more commonly as a sequence of the overflow of rivers. The exact significance of flooding has yet to be explained, but there is, as Christophers remarks, reason to believe that it must be something more than the provision of unusual facilities for the multiplication of anophelines.

But whilst this subject requires further elucidation there is no room for doubt that flooding is an important factor determining the *site* of these epidemics within those areas otherwise predisposed to them.

The effect of famine and lesser degrees of economic stress, mentioned by Christophers, is another factor which will be referred to more fully under the next heading. It is only necessary here to state that any lowering of resistance of the human host may well tend to disturb still further that equilibrium between immunity and infection which is such an important factor in the production of fulminant malaria.

It is necessary now to offer some explanation of the apparent paradox that a high degree of endemicity affords no protection against a fulminant epidemic. In the first place, so far as the Punjab is concerned, there are no records of the spleen-rate previous to the 1908 epidemic. It is clear also that the height of the spleen-rate is of little importance

from the immunity point of view, the important point is the *amount of reduction it has undergone.* To quote a concrete case : in a certain portion of Amritsar city the spleen-rate varied between 75 to 100 per cent. in 1909. It was the worst affected area in the previous epidemic and it subsequently exhibited the highest spleen-rate.

In 1913 it still had the *relatively* highest spleen-rate, not only in children of 6—12 years of age, but also in children born since 1908. The spleen-rate, however, was then less than 35 per cent. It may be anticipated that at the next epidemic this area will suffer as much as, if not more than, other parts of the city. For there will be present a large number of children extremely susceptible to the disease and even the adults will be more susceptible than they were after the previous epidemic. Further, in this area, the spleen-rate being higher than elsewhere, a larger proportion of anophelines will presumably become infected than in areas with a lower spleen-rate.

It is, therefore, not difficult to understand how in an area with a *relatively* high spleen-rate a fulminant epidemic will be associated with an infantile mortality and an adult death-rate greater than in areas with a lower splenic index.

IX.—The Mechanism of Epidemic Malaria.

It is not proposed to consider in detail the mechanism of those epidemics which in Part I have been defined as being exaggerations of the normal seasonal incidence of the disease which are apt to occur at irregular intervals either as localised or generalised epidemics. In view, however, of the resemblance of the latter to fulminant malaria it is necessary to indicate briefly the reasons for according them a distinctive appellation and a separate description.

In the first place, it has been shown in Section III, that both generalised and localised epidemics may occur indiscriminately in the tropical and sub-tropical zones. Secondly, no association has been found to exist between them and the overflow of rivers and excessive rainfall. Thirdly, they may be extremely localised as in the case of those epidemics which Christophers and Bentley have shown to be so frequently associated with the aggregation of labour. Fourthly, they do not appear to occur with cyclical regularity in any given area; and finally they may and do occur in consecutive years in the same area. But in spite of these differences their mechanism of production is essentially of the same nature, from the point of view of malarial immunity, as that of fulminant epidemics.

This point is of importance since if the occurrence of a fulminant epidemic is a phenomenon associated with the mechanism of immunity, it is probable that all epidemic manifestations of malaria will have a similar origin.

In the case of fulminant malaria it has been shown that climatic conditions interfere with the mechanism necessary to maintain "equilibrium," this manifestation of malaria therefore occurs in the areas and in the circumstances already detailed. In the case of malarial epidemics of the nature now under consideration it is possible that "equilibrium" may be disturbed in another manner. Here comes in the "human factor" first prominently brought to notice by Christophers and Bentley.

Under conditions of economic stress, exposure, hard work, overcrowding and underfeeding every condition favourable to relapses is present.

On the other hand, as the above authors have shown, these circumstances are exceedingly favourable to infection. It is thus not difficult to understand how under conditions of "tropical aggregation of labour" an epidemic may break out owing to the combined effect of an increase in the amount of local infection being associated with a depression in the powers of vital resistance.

As such circumstances may occur in any endemic part of the world it follows that these epidemics may show a similar distribution and, indeed, as has been mentioned, they have been met with as far north as Chifu in North China and as near the equator as Ceylon. It is therefore believed that the part played by immunity in fulminant malaria may, under somewhat different circumstances, be responsible for generalised or localised epidemics. There appears indeed to be little real difference between all epidemic manifestations of the disease but, for reasons already detailed, it seems expedient to differentiate clearly between fulminant malaria and other manifestations of malaria in epidemic form.

X.—Certain Applications of the Theory of Malarial Immunity.

This investigation was originally undertaken in order to attempt to throw some light on the mechanism of fulminant malaria as met with in the Punjab. During its course, however, the important part played by immunity came into prominence. It was, therefore, decided to widen the scope of the investigation with a view to seeing whether the mechanism of malarial immunity, advanced in this paper,

is applicable under other conditions ; for it is obvious that if any fundamental principle of immunity is at work in producing these epidemics it must be in operation in all circumstances.

The author has had no opportunity of studying malaria except in regions subject to fulminant epidemics so that his remarks in regard to other areas are entirely founded on the work of others, and his conclusions are largely of a speculative nature. This part of the research, however, serves a useful purpose since it shows in brief outline how the mechanism of immunity described in this paper may be applied to other manifestations of malarial infection. This has already been done in the case of tropical, sub-tropical and epidemic malaria, and it is now proposed to attempt to apply it to certain other aspects of the malaria problem.

(A).—*Malaria and Blackwater Fever.*

Christophers and Bentley(12) have brought forward strong evidence to show that blackwater fever is an epiphenomenon of " intense malaria." Some authorities still hesitate to accept this view and they point to the fact that whilst nowhere is malaria, at times, more severe than in the Punjab, yet blackwater fever is not commonly met with in that Province. It has been stated that the disease occurs in the Punjab, but it may be taken as an undoubted fact that blackwater fever is excessively rare—even if it occurs at all—in the Punjab *plains.* But Christophers and Bentley, in addition to bringing out the fact that intensity of infection is an essential precursor of blackwater fever, show that length of residence in a blackwater fever country is also an important factor.

These investigators found, both in the case of Europeans and Bengalis living in the Duar tract, that there is a marked tendency for the first attack of blackwater fever to occur about 18 months to two years after arrival in this area.

Stress is also laid on the fact that the local conditions in regard to malaria are such that the inhabitants are exposed to inoculation with sporozoits for a greater portion of the year. The conditions are, therefore, very different from those met with in the Punjab where the " fever season " is usually reckoned to last about 3 months. Blackwater fever, therefore, in addition to being associated with " intense malaria," may be limited to areas where something approaching perennial infection may occur. If this surmise be correct then not only does it cease to be a matter for surprise that blackwater fever does not occur in the Punjab

plains, but we are justified in asserting that blackwater fever and fulminant malaria may not be expected to co-exist in the same locality.

(*B*).—*The Influence of Malarial Immunity on Anti-malarial Measures.*

The practical results which follow an acceptance of the theory of malarial immunity propounded in this paper are of considerable importance, for it will be necessary to modify our anti-malarial measures in order to meet the conditions which this theory appears to show must be fulfilled if malaria is to be combated with success. In the first place, in connexion with tropical malaria, it becomes clear that all anti-malarial measures must be of an extremely permanent nature, otherwise, by causing fluctuations in immunity they may do more harm than good.

In the case of sub-tropical malaria it must now be recognised that in certain areas great fluctuations in malaria and in the spleen-rate occur naturally. This fact obviously will have to be taken into account when appraising the results of anti-malarial measures. In such localities also the use of the terms "healthy," "moderately endemic," "highly endemic" and "hyper-endemic," as recommended by the Central Committee for the Study of Malaria in India,(43) to signify localities with spleen-rates of various percentages, become inapplicable. It is suggested that in their place it will be expedient to estimate the "reduction factor" or the percentage of reduction which the spleen-rate undergoes during a given period such as five years.

In connexion with fulminant malaria the outcome of this research gives promise of practical results in the reduction of malaria in the Punjab. Its prevention or mitigation is *par excellence* the malaria problem in this province, for an examination of Chart 1 shows that, but for fulminant epidemics, malaria in the Punjab would be a matter of comparative insignificance, at any rate so far as mortality is concerned. The use of quinine, except as a temporary expedient, is out of the question or even if the whole "world-supply" were available and people were willing to take it, it would not suffice to prevent an enormous mortality during a big epidemic. Further, minor anti-malarial measures including anti-mosquito campaigns will also be of little avail in preventing these epidemics, for it has been shown that they are intimately associated with floods which for the most part are not of local origin.

The control of these floods is, therefore, the key to the malaria problem of the Punjab. Malaria surveys now being undertaken in various places have shown that flooding is often dependent, not on the overflow

of large rivers, but on flood water flowing from the hills along the natural drainage channels of the country, in lines parallel to the rivers into which it for the most part eventually finds its way. These natural drainage channels have in some cases been obstructed for agricultural purposes, in others canals and railways have cut across their path, with the result that flood waters are diverted over the land and form those vast sheets of water which are the immediate precursors of these outbreaks.

It appears essential that maps showing the natural drainage channels of the country should be prepared, that a small permanent department should be formed whose duty it will be to clear these channels, to provide an ordered outlet for flood water generally, and last but not least to see that these channels are not obstructed in the future.

Finally the prophylactic use of quinine may require to be modified in order to comply with this theory of malarial immunity, for it seems probable that insufficient dose or doses administered at too long intervals may have undesirable effects, for in these circumstances the "equilibrium" between infection and immunity may be upset with the result that an attack of malaria may follow. Perhaps it is on these lines that those not uncommon cases where the prophylactic use of quinine has appeared useless may be explained. Thus Thompson(44) as the result of an experiment carried out at Lucknow states that "experience and careful experiment have taught that prophylactic quinine is useless and perhaps harmful." He shows that in 1911 the admission rates for fever of two British regiments taking quinine in doses of ten grains on two consecutive days each week, were 97 and 57 per 1,000, respectively, whilst the rate for a regiment *not* taking quinine was only 33 per 1,000.

Many other obscure points in the epidemiology of malaria appear to be explained by the theory of malarial immunity put forward in this paper. For example, Strong(45) records that in Papua the inhabitants of hyper-endemic areas do not suffer from "fever" whilst in their own homes, but only when they visit localities where malaria is either mild or absent. Major Perry(46) also informs me that this is commonly stated to be a well known fact amongst the aborigines of the Jeypore hill tract in Madras. In this case it is possible that in the absence of the accustomed amount of fresh infection equilibrium between the degree of immunity and the amount of infection is temporarily disturbed.

Enough has been said to indicate the wide application and great importance of the part attributed to malarial immunity. It is believed

that it suffices to explain the various epidemic manifestations of the disease and that it is no longer necessary to refer these epidemics, in the words of Celli,(47) to "marvellous intrinsic properties of living protoplasm much more than the eventual concomitance of such extrinsic factors as climate."

XI.—Summary of Conclusions.

The following conclusions summarise the main points that this study of malaria from the epidemiological aspect appears to justify.

(A).—*General.*

(1) Endemic malaria may be divided into (*a*) Tropical Malaria; (*b*) Sub-tropical Malaria.

(2) Malaria may manifest itself in epidemic form as (*a*) Fulminant malaria; (*b*) Generalised epidemic malaria; (*c*) Localised epidemic malaria.

(3) Fulminant malaria is ordinarily a manifestation of sub-tropical malaria.

(4) The principle underlying the occurrence of these various manifestations of malaria is closely related to the subject of immunity.

(B).—*Malarial Immunity.*

(5) Immunity in malaria appears ordinarily to be an acquired partial immunity which manifests itself as a relative tolerance to the effects of malarial infection.

(6) Whilst the protection afforded by a single infection is slight and not long maintained in the absence of reinfection, a high degree of tolerance to malarial infection is brought about as the result of *repeated inoculation* with fresh parasites.

(7) In circumstances where perennial infection may occur the collective immunity of a community tends ordinarily to remain fairly constant, whilst it is subject to marked fluctuations in localities where the transmission of infection remains in abeyance over prolonged periods.

(8) All epidemic manifestations of malaria are ultimately dependent upon "equilibrium" between the degree of immunity and the amount of infection being temporarily disturbed or lost.

(9) The spleen-rate of a community may be utilised as an index of the tolerance to malaria possessed by that community; a spleen-rate

remaining constant over a period of years ordinarily signifies a constant immunity, whilst a fluctuating spleen-rate implies corresponding oscillations in the degree of immunity possessed by the community.

(C).—*Tropical Malaria.*

(10) Tropical malaria is associated with conditions which render possible the transmission of fresh malarial infection almost throughout the whole year. In such circumstances tolerance to infection remains fairly constant and there is little or no tendency for pernicious forms of malaria or for fulminant epidemics to occur *amongst the indigenous inhabitants.*

(11) The spleen-rate of such communities ordinarily remains fairly constant and, in addition to affording evidence of the endemic prevalence of the disease, its constancy over a period of years indicates that the immunity of the community likewise remains fairly constant.

(12) Generalised or localised epidemics of malaria may occur in tropical countries as the result of conditions causing a marked temporary increase in the amount of local infection.

(13) An epidemic of a fulminant nature may follow the introduction of malaria into non-endemic tropical areas, but such epidemics may not be expected to recur after the disease has established itself in its new habitat.

(D).—*Sub-Tropical Malaria.*

(14) Endemic malaria occurring in localities in which owing to climatic circumstances the active transmission of malaria is subject to prolonged periods of interruption constitutes sub-tropical malaria. In these areas, owing to the mechanism of malarial immunity "equilibrium" between infection and immunity is maintained with more difficulty than in tropical countries.

(15) Marked spontaneous fluctuations in the spleen-rate over a period of years are of frequent occurrence in connexion with sub-tropical malaria.

(16) The use of the terms " healthy," " moderately endemic," " highly endemic " and " hyper-endemic " to indicate spleen-rates of various percentages may be inapplicable in the case of sub-tropical malaria. In these circumstances the *periodical* estimation of the spleen-rate and the calculation of its " percentage reduction " over a period of years will afford information of considerable value.

(E).—*Fulminant Malaria.*

(17) Fulminant malaria is apt to occur in localities where the active transmission of malaria is annually subject to prolonged periods of interruption.

(18) " Interruption " of infection is associated with a decrease in tolerance to malarial infection, as the result both of the absence of reinfection and of the elimination of residual infection.

(19) A fulminant epidemic occurs in circumstances in which a great relative decrease in immunity is associated with a marked temporary increase in the amount of infection.

(20) *A great decrease in relative immunity* occurs in areas where the physiographical conditions are normally so unfavourable to endemic malaria that the spleen-rate spontaneously undergoes a great diminution during a short period of years.

(21) *A marked temporary increase in the amount of infection* may occur periodically in such areas as the result of excessive rainfall and " flooding " producing conditions abnormally favourable to the malaria parasite and to its transmission from man to man.

(22) The exact significance of flooding still remains to be elucidated but it is probable that the unusual facilities that it affords for the multiplications of anophelines is not its sole influence.

(23) The immunity conferred by a fulminant epidemic slowly disappears, but may become greatly reduced in about five years. As the result of this circumstance fulminant epidemics may be expected to occur usually at intervals of not less than the above period.

(24) A *relatively* high spleen-rate compared with other areas affords no protection against a fulminant epidemic as it is not the height of the spleen-rate but the *amount of reduction* it has undergone that is of paramount importance.

(25) A low spleen-rate in an area subject to fulminant malaria may have a widely different significance to a similar spleen-rate in a tropical country. In the case of the former a fulminant epidemic may be anticipated to follow the next occurrence of flooding, whilst in a tropical area no such effect will be produced.

(26) Fulminant malaria is more particularly the result of infection with the malignant tertian or tropical parasite.

(27) The mitigation and even prevention of fulminant epidemics may be predicted to follow the carrying out of measures designed to prevent the occurrence of flooding.

(F).—*Epidemic Malaria.*

(28) Epidemics of malaria, either generalised or localised, may occur in any part of the endemic area of malaria without reference to climatic circumstances. They are associated with conditions which either *temporarily* increase the amount of local infection or lower the immunity of the community and more particularly with conditions which do both.

(29) In spite of the mutual dependence of these epidemics and fulminant malaria on loss of "equilibrium" between the amount of infection and the degree of immunity, the fact that they possess no other characteristics in common renders it expedient to differentiate them from one another.

APPENDIX.

The spleen-rates mentioned in this paper were determined by an examination of children between two and ten years of age. The numbers examined and other details, where known, are given below.

	Area.	Population, 1911.	Year.	No. of children examined.	Spleen-rate percentage.	Name of observer.
1.	Kathala Village	About 800	1908	Unknown	77	Maj. E. L. Perry, I.M.S.
2.	Ditto	Ditto	1909	267	75	ditto.
3.	Ditto	Ditto	1910	78	59	ditto.
4.	Ditto	Ditto	1912	130	20	ditto.
5.	Ditto	Ditto	1913	120	10	Capt. C. A. Gill, I.M.S.
6.	Gujrat Town	18,692	1909	57	43	Maj. S. R. Christophers, I.M.S.
7.	Ditto	18,692	1914	1,200	3	Capt. C. A. Gill, I.M.S.
8.	Bhera Town	15,202	1909	113	84	Maj. S. R. Christophers, I.M.S.
9.	Ditto	15,202	1914	857	25	Capt. C. A. Gill, I.M.S.
10.	Miani Town	5,819	1909	56	79	Maj. S. R. Christophers, I.M.S.
11.	Ditto	5,819	1914	277	15	Capt. C. A. Gill, I.M.S.
12.	Amritsar City	152,756	1909	1,253	63	Maj. S. R. Christophers, I.M.S.
13.	Ditto	152,756	1913	3,047	15	Capt. C. A. Gill, I.M.S.
14.	Batala Town	26,430	1914	1,213	2	ditto.
15.	Palwal Town	9,485	1909	147	88	Maj. S. R. Christophers, I.M.S.
16.	Ditto	9,485	1913	247	17	Capt. S. Webb, I.M.S.
17.	Palwal Villages	Unknown	1909	133	82	Maj. S. R. Christophers, I.M.S.
18.	Ditto	Unknown	1913	868	17	Capt. S. Webb, I.M.S.
19.	Hodel Town	5,468	1910	230	57	Maj. S. R. Christophers, I.M.S.
20.	Ditto	5,468	1913	298	15	Capt. S. Webb, I.M.S.
21.	Aatri	About 2,000	1909	41	81	Maj. S. R. Christophers, I.M.S.
22.	Ditto	About 2,000	1914	136	30	Capt. C. A. Gill, I.M.S.

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The author is under great obligations to Major S. R. Christophers' monograph "Malaria in the Punjab," from which frequent quotations have been made. He is also indebted to Major Christophers personally for the reference to the interesting Merv epidemic and for much valuable advice concerning the preparation of this paper.

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